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(54) Transdermal delivery system.

(57) A transdermal delivery system (1,11) for the transdermal administration of a drug has

(a) a backing (2,12) that is substantially impermeable to the drug,

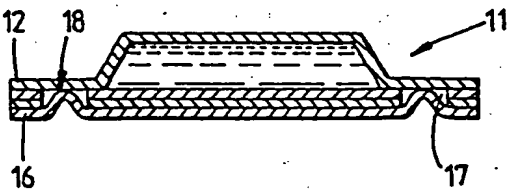
(b) a matrix (3,13), adjacent to a surface of the backing, the matrix containing a gel comprising a hydrophilic fluid, a fluid gelling agent and the drug, and

(c) a perforated sheet (4,14), adjacent to the matrix, that allows passage of the drug containing gel through its perforations.

Preferably the system also has a contact adhesive layer (5,15) and a protecting layer (6,16).

The long term adhesion of the delivery system to a patient may be effected by forming a channel (17), surrounding the matrix, in the perforated sheet/contact adhesive layer lamina. The channel inhibits the lateral movement of the drug containing gel. Furthermore, by forming a weak seal (18) in the matrix surrounding channel, the loss of a volatile drug from the gel may also be prevented.

Fig. 3.



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Patentansprüche:

1. Wirkstoffpflaster zur kontrollierten Abgabe von Arzneistoffen an die Haut, bestehend aus einer Deckschicht, einem damit verbundenen, wasserunlöslichen Klebefilm aus einer Kautschuk/Klebeharzmasse, in der der beziehungsweise die Wirkstoffe löslich oder teilweise löslich ist beziehungsweise sind, und einer den Klebefilm abdeckenden, wieder ablöslichen Schutzschicht, dadurch gekennzeichnet, daß der beziehungsweise die Wirkstoffe in der Kautschuk/Klebeharzmasse zusammen mit einem in Wasser quellbaren, im Klebefilm nicht löslichen Polymeren in einer Menge von 3 bis 30 Gew.-%, bezogen auf die Kautschuk/Klebeharzmasse, vorliegt.

2. Wirkstoffpflaster gemäß Anspruch 1, dadurch gekennzeichnet, daß als Arzneistoffe ß-Blocker, Steroidhormone, Calciumantagonisten und herzwirksame Medikamente verwendet werden.

3. Wirkstoffpflaster gemäß Anspruch 1 oder 2, dadurch gekennzeichnet, daß das in Wasser quellbare Polymere ein Polysaccharid oder Polysaccharidgemisch ist, wie z.B. Galaktomannan, Cellulose, Tragant.

4. Wirkstoffpflaster gemäß einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die Kautschuk/Klebeharzmasse unterteilt ist zwischen einer Wirkstoff und das in Wasser quellbare Polymere enthaltenden Reservoirschicht und einer gegebenenfalls Wirkstoff enthaltenden Haftklebeschicht, wobei zwischen der Reservoirschicht und der Haftklebeschicht eine Trennschicht vorgesehen ist, die für die Kautschuk/Klebeharzmasse und darin gelöstem Wirkstoff durchlässig, für das in Wasser quellbare Polymere völlig oder im wesentlichen undurchlässig ist.

5. Wirkstoffpflaster für Estradiol gemäß einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das in Wasser quellbare Polymere ein Galaktomannan ist.

hydroxyethyl cellulose sold by Hercules Powder Company under the Trade Mark Natrosol 250 is especially suitable for use in the pres nt gel.

Th amount of cellulosic material employed in the gel of the present delivery system is determined by th rate of (and efficiency of) drug release that is required. Preferably the amount of cellulosic material used will be between 1% and 6%, especially between 2.5% and 3.5%, by weight of the total gel.

Although, in preferred embodiments of the present transdermal system, the cellulosic material in the gel is hydrated by water only, minor quantities of polar, biologically acceptable solvents (especially alcohols) may be present in the hydrating medium without detriment to the delivery system.

(b) Water-soluble polysaccharides, such as agar, agarose, algin, sodium alginate, potassium alginate, carrageenan, kappa-carrageenan, lambda-carrageenan, fucoidan, furcellaran, laminaron, gum tragacanth, hypnea, eucheuma, gum arabic, gum ghatti, gam karaya, guar gum, locust bean gum, quince psyllium, okra gum, arabinogalactin, perctin, xanthan, scleroglucan, dextran, amylose, amylosepectin, dextrin and the like.

(c) Silicon containing materials, such as fumed silica, reagent grade sand, precipitated silica, amorphous silica, colloidal silicon dioxide, fused silica, silica gel, quartz and particulate siliceous materials commercially available (e.g. Syloid (Trade Mark), Cabosil (Trade Mark), Aerosil (Trade Mark) and Whitelite (Trade Mark)).

The amount of silicon material used in the present gel is preferably between 0.1% and 25%, especially between 1% and 15%, by weight of the total gel.

(d) Long chain (C_8-C_{26}) fatty alcohols, such as cetyl alcohol, stearyl alcohol and cetostearyl alcohol.

The gel may also contain minor quantities of a suitable preservative, for example Octhilinone - (Kathon, Trade Mark).

Any drug that is compatible with the fluid and the fluid gelling agent and that can be administered percutaneously through the skin for passage into the systemic circulation may be incorporated into the present delivery system.

Examples include:

(a) Vasodilators, such as glyceryl nitrate, amyl nitrate, isosorbide mono-and dinitrate, triethanolamine trinitrate, nifedipine, verapamil, nicotinic acid,

(b) Antihypertensives, such as clonidine, propranolol,

(c) Diuretics, such as hydrochlorothiazide, bendrofluazide, ethacrynic acid,

(d) Antihistamines, such as 2-diphenylmethoxy-N, N-dim thylethanamine, clemastine fumarate, mepyramine,

(e) Anticholinergics, such as scopolamine, atropine, methscopolamine bromide,

(f) Analgesics, such as codeine, morphine, aspirin, sodium salicylate, salicylamide, hydromorphone, phenazocine

(g) Bronchodilators, such as salbutamol, alpha-(1-(methylamino) ethyl)-benzenemethanol, isoprotenerol,

(h) Steroids, such as 6-methylprednisolone, methyltestosterone, fluoxymesterone, estrone, estradiol, ethinylestradiol, 17-hydroxyprogesterone acetate, medroxyprogesterone acetate, 19-norprogesterone, norethindrone, hydrocortisone, dexamethasone, prednisolone,

(i) Non-steroidal hormones, such as thyroxine, vasopressin, heparin, insulin,

(j) Antidiabetics, such as chlorpropamide, glibenclamide,

(k) Antimalarials, such as 4-aminoquinolines, 9-aminoquinolines, pyrimethamine,

(l) Vitamins, Essential Amino Acids and Essential Fats,

(m) Sedatives and Hypnotics, such as pentabarbital sodium, phenobarbital, sodium phenobarbital, secobarbital sodium, carbromal,

(n) Psychic energisers, such as 3-(2-aminopropyl)indole acetate and 3-(2-aminobutyl)-indole acetate,

(o) Tranquilisers, such as reserpine, chlorpromazine hydrochloride, thiopropazate hydrochloride,

(p) Antimicrobials, such as penicillins, tetracyclines, oxytetracyclines, chlortetracyclines, chloramphenicol, sulphonamides,

(q) Antiinflammatorys, such as indomethacin and ibuprofen,

Of the above materials, nitroglycerine, nifedipine, salbutamol and hydromorphone are particularly preferred for use in the present delivery system.

It will be appreciated that the drug may be added to the above matrix not only in the form of the pure chemical compound, but also in admixture with other drugs which may be transdermally applied or with other ingredients which are not incompatible with the desired objective of transdermally administering the drug to a patient. Thus, simple pharmacologically acceptable derivatives of the drugs, such as ethers, esters, amides, acetals, salts and the like may be used. In some cases such derivatives may actually be preferred.

im Klebefilm nicht lösliche Polymere ein Galaktomannan ist.

13. Verfahren gemäß einem der Ansprüche 9 bis 11, dadurch gekennzeichnet, daß der Wirkstoff Bupranolol und das in Wasser quellbare, im Klebefilm nicht lösliche Polymere mikrokristalline Cellulose ist.

14. Verfahren gemäß einem der Ansprüche 9 bis 11, dadurch gekennzeichnet, daß der Wirkstoff Nitroglycerin und das in Wasser quellbare, im Klebefilm nicht lösliche Polymere mikrokristalline Cellulose ist.

15. Verfahren gemäß einem der Ansprüche 9 bis 11, dadurch gekennzeichnet, daß der Wirkstoff Propranolol und das in Wasser quellbare, im Klebefilm nicht lösliche Polymere mikrokristalline Cellulose ist.

i.e. which inhibits the lateral movement of the drug containing gel. In this way the outer (circumferential) portion of the rate controlling sheet/adhesive layer lamina is kept free from the matrix's contents. This in turn ensures that the skin adhesion of this outer portion (at least) remains high.

In the second aspect, the loss of a volatile constituent from a delivery system having a channel surrounding the matrix (as described above) is prevented by forming a surrounding (circumferential) seal, between the backing and the protecting layer, in this matrix surrounding channel.

In order to facilitate the manufacture of the present transdermal delivery system there is also provided, in a further aspect of the present invention, a process for the preparation of a transdermal delivery system comprising mixing a fluid, a fluid gelling agent and a drug to form a drug containing gel.

The drug containing gel may then be incorporated in the present delivery system by depositing the gel on a perforated sheet, optionally, having attached thereto an adhesive layer and a protecting layer. The system may be completed in this case by heat sealing a backing (over the gel) to the perforated sheet.

Alternatively the gel may be deposited on the backing, in which case the perforated sheet may be heat sealed (over the gel) to the backing. In the case of perforated sheet delivery systems having no surrounding channel (in the perforated sheet/adhesive layer lamina), the system may be prepared on a conventional sachet machine. This represents a major advantage of the present invention.

The present transdermal delivery system and processes for its preparations will now be described by way of example only, with particular reference to the Figures in which:

Figure 1 is a cross-sectional view of a transdermal delivery system according to the present invention,

Figure 2 is a cross-sectional view of a transdermal delivery system according to this invention in which the matrix is surrounded by a channel,

Figure 3 is a cross-sectional view of a transdermal delivery system according to this invention in which the backing and the protecting layer are sealed in the matrix surrounding channel, and

Figure 4 is the nitroglycerin plasma level achieved (as a function of time) by six patients using a delivery system according to the present invention.

Example 1

Gel Preparation

0.7g of Nitroglycerin (in the form of 10% TNG on lactose (BP)) and 0.1g of Octhilinone (Kathon CG, Trade Mark) were dissolved in distilled water (89.9g), by magnetic stirring in a covered vessel warmed to a temperature between 25¤ and 45¤C.

When a clear solution was formed, hydroxyethyl cellulose (Natrosol 250 HHBR, Trade Mark, 3g) was added slowly with stirring. After the addition of the hydroxyethyl cellulose was completed, stirring was continued for a further 5 mins until a cohesive gel had formed.

Delivery System Preparation

An aluminium backing (3M 1006, Trade Mark) was heat sealed to a lined, self adhesive ethylene/vinyl acetate copolymer (EVA) macropore membrane (3M 1527L, Trade Mark) to form a 10 cm^2 elliptical delivery system with one end open. 2.3g of the above gel was then injected into the system's matrix via a tube attached to a syringe. The ellipse was then closed by further heat sealing, and the delivery system was cut to shape, allowing a protruding tab of the release liner.

The delivery system was stored in a heat sealed aluminium foil envelope.

Example 2

The delivery system of Example 1 was prepared except that isosorbide dinitrate on lactose replaced the TNG on lactose.

Example 3

The delivery system of Example 1 was prepared except that octyl nitrate (0.7g) replaced the TNG on lactose, the gel being made up to 100gm in weight oy the addition of distilled water.

Example 4

The delivery system of Example 1 was prepared except that isosorbide mononitrate replaced the TNG on lactose.

Example 5

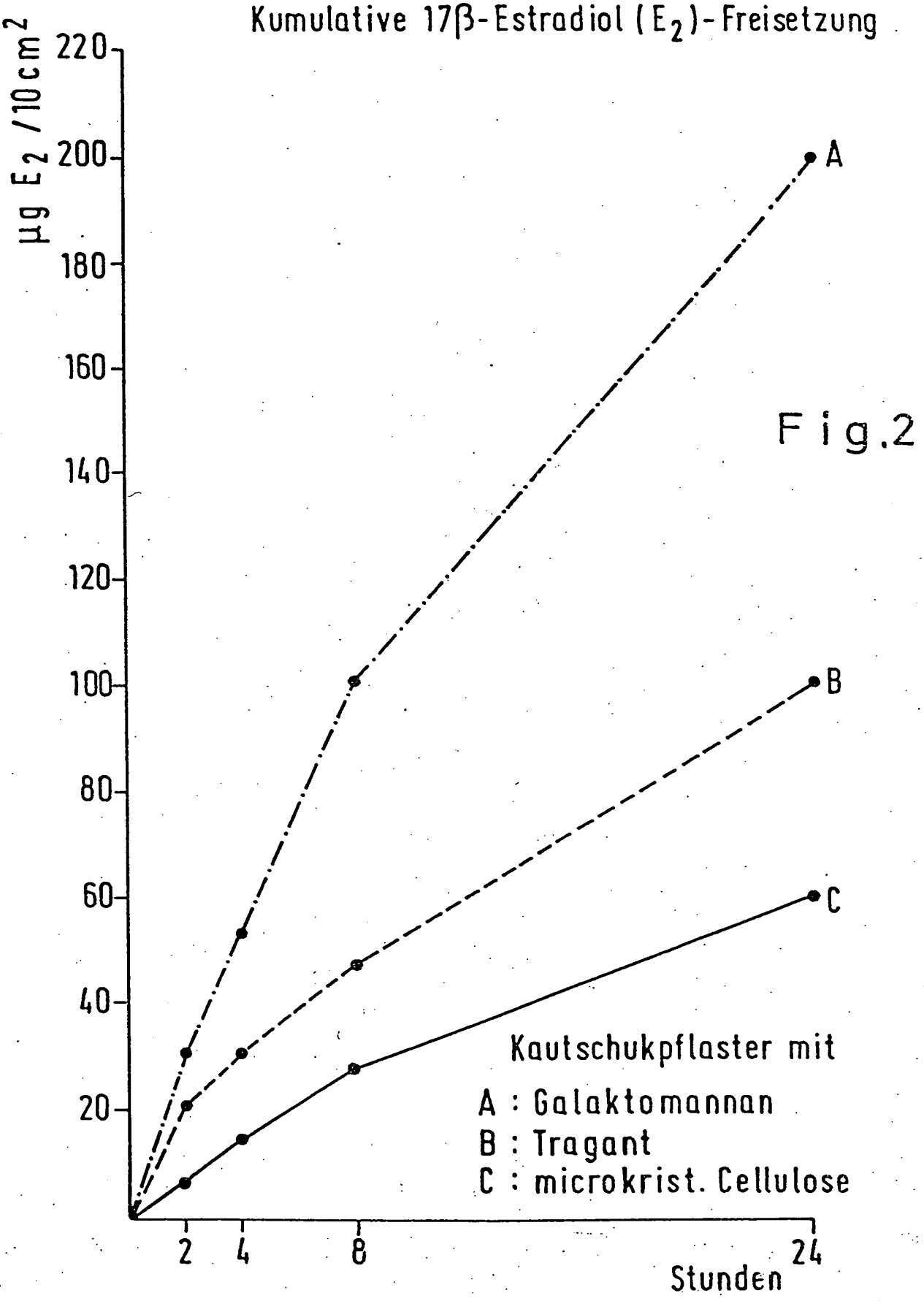

Kumulative 17β-Estradiol (E_2)-Freisetzung
µg E_2 /10cm^2
220
200
180
160
140
120
100
80
60
40
20
A
B
C
2
4
8
24
Stunden
Kautschukpflaster mit
A : Galaktomannan
B : Tragant
C : microkrist. Cellulose

Fig.2

(a) a backing that is substantially impermeable to the drug,

(b) a matrix, adjacent to a surface of the backing, the matrix comprising a drug containing gel comprising a fluid, a fluid gelling agent and the drug, and

(c) a sheet, adjacent to the matrix, that controls the rate of gel release from the system, characterised in that the rate controlling sheet is a perforated sheet that allows passage of the drug containing gel through its perforations.

2. A transdermal delivery system according to claim 1 characterised in that the rate of diffusion of the drug through the sheet (other than through the perforations) is below about $150\mu ghr^{-1}cm^{-2}$.

3. A transdermal delivery system according to either claim 1 or claim 2 characterised in that the perforated sheet comprises an ethylene-vinyl acetate copolymer.

4. A transdermal delivery system according to claim 3 characterised in that the perforated sheet has a thickness between 0.1 and 0.4mm.

5. A transdermal delivery system according to anyone of claims 1 to 4 further comprising, in contact with the perforated sheet, a contact adhesive layer and, in contact with the adhesive layer, a protecting layer.

6. A transdermal delivery system for the transdermal administration of a drug comprising

(a) a backing that is substantially impermeable to the drug,

(b) a matrix, adjacent to a surface of the backing, the matrix comprising a drug containing gel comprising a fluid, a fluid gelling agent and the drug,

(c) a sheet, adjacent to the matrix, that controls the rate of drug or gel release from the system,

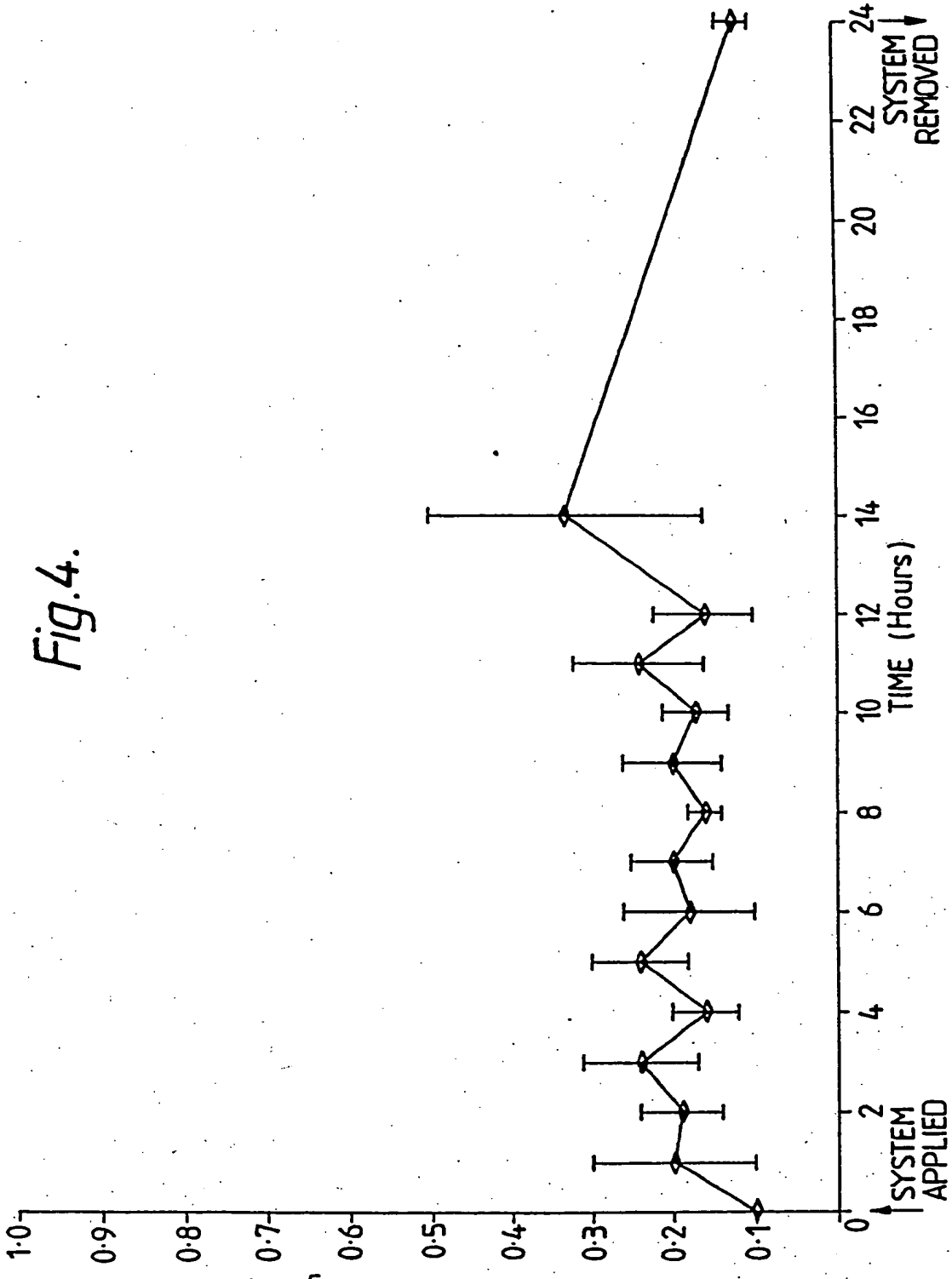
(d) in contact with the rate controlling sheet, a contact adhesive layer, and

(e) in contact with the adhesive layer, a protecting layer characterised in that the matrix is surrounded by a channel, formed in the rate controlling sheet and the contact adhesive layer, which inhibits the lateral movement of the drug containing gel.

7. A transdermal delivery system according to claim 6 characterised in that the matrix is surrounded by a seal, between the backing and the protecting layer, in the matrix surrounding channel.

8. A transdermal delivery system according to either claim 6 or claim 7 characterised in that the rate controlling sheet is a perforated sheet that allows passage of the drug containing gel through its perforations.

Fig.4.


CONCN OF NITROGLYCERIN (ng/ml)
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (Hours)
SYSTEM APPLIED
SYSTEM REMOVED

Europ an Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 86 30 3220

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
P,X	EP-A-0 171 800 (ALLPACK) * Figures 1-4 * -----	6-8	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	25-09-1986	RAKOWICZ,J.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken al ne
Y : particularly relevant if combined with another document of the same categ ry
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member f the same patent family, corresponding document

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been proposed to improve the penetration rate of the pharmacologically active agent through the skin. However, most systems do not provide a sufficient penetration rate of the pharmacologically active agent or suffer from other disadvantages. Before the priority date of the present application the transdermal pharmaceutical compositions for systemic administration of drugs commercially available on a wide scale were restricted to pharmacologically active agents which exist in liquid form e.g. scopolamine or nitroglycerin, and which in any event easily penetrate the skin.

There is thus a need for new approaches to the transdermal application of solid and liquid pharmacologically active agents using controlled release systms.

We have now surprisingly found that the pharmacologically active agent bopindolol, 4-(2-benzoyloxy-3-tert-butylaminopropoxy)-2-methylindole, a beta-blocker which is known for oral administration e.g. for the treatment of hypertension, and methysergide (9,10-didehydro-N-[1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8-carboxamide, a known serotonin antagonist e.g. for the prophylaxis of migraine, have especially interesting properties for transdermal administration. These are hereinafter referred to as the active agents of the invention.

The penetration of these active agents through the skin may be observed in standard in vitro or in vivo tests.